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Epilepsia Partialis Continua responsive to neocortical electrical stimulation

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Epilepsia Partialis Continua responsive to neocortical electrical stimulation

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ABSTRACT

Epilepsia partialis continua (EPC), defined as a syndrome of continuous focal jerking, is a rare form of focal status epilepticus which usually affects a distal limb and when prolonged, can produce long-lasting deficits in limb function. Substantial electrophysiological evidence links the origin of EPC to the motor cortex, thus surgical resection carries the risk of significant handicap. We present two patients with focal, drug-resistant EPC who were admitted for intracranial video-electroencephalography monitoring to elucidate the location of the epileptogenic focus and identification of eloquent motor cortex with functional mapping. In both cases, the focus resided at or near eloquent motor cortex and therefore precluded resective surgery. Chronic cortical stimulation delivered through subdural strips at the seizure focus (continuous stimulation 60-130Hz 2-3mA) resulted in >90% reduction in seizures and abolition of the EPC after a follow-up of 22 months in both patients. Following permanent implantation of cortical stimulators, no adverse effects were noted. EPC re-started when intensity was reduced or batteries depleted. Battery replacement restored previous improvement. This two-case report opens up avenues for the treatment of this debilitating condition.

INTRODUCTION

Epilepsia partialis continua (EPC), also known as Kojevnikov's epilepsy is a rare form of focal motor status epilepticus.¹ It is defined as "spontaneous regular or irregular clonic muscular twitching affecting a limited part of the body, sometimes aggravated by action or sensory stimuli, occurring for a minimum of one hour, and recurring at intervals of no more than ten seconds".^{2,3} Some authors demand coexistent electrophysiological evidence of cortical origin in the form of EEG abnormalities or giant somatosensory evoked potentials (SSEPs).⁴ Aetiology can be inflammation/immune mediated (vasculitis, cerebral venous thrombosis, Rasmussen's encephalitis), neoplasms, trauma, and metabolic disorders. In up to 28% of cases aetiology remains cryptogenic.⁴

EPC is commonly resistant to anticonvulsant drugs. Surgical resection is an alternative, but it is usually fraught with morbidity as the epileptogenic cortex is often in the vicinity of eloquent cortex. Some techniques related to neuromodulation have been tried for the treatment of EPC and status epilepticus, for instance, vagal nerve stimulation,⁵ thalamic deep brain stimulation,⁶ and repetitive transcranial magnetic stimulation.⁷ In addition, recent studies have shown efficacy using chronic subthreshold cortical stimulation in patients with focal epilepsy from the primary motor cortex.^{8,9,10}

This report includes the two patients with drug-resistant EPC who underwent permanent implantation of a cortical stimulator system at King's College Hospital. Both patients were admitted for intracranial video-electroencephalography monitoring to elucidate the location of the epileptogenic focus and identification of eloquent motor cortex with functional mapping. In both cases, the focus resided at or near eloquent motor cortex and therefore precluded resective surgery. Permanent subdural stimulation strips were implanted at the seizure focus and connected to a stimulator implanted in the chest. Continuous electrical stimulation with 0.45 ms pulses of up to 3 mA (the strongest pulse parameters allowed by the stimulation system) was applied at 60 or 130 Hz to the areas showing discharges during previous intracranial monitoring. These stimulation frequencies were chosen based in our experience

with deep brain stimulation for epilepsy.¹¹ No motor responses or tetany were associated with such stimulation parameters.

Case 1

Clinical History: A 21-year-old right handed male with background history of mild learning difficulties and hypomelanosis of Ito presented for evaluation of EPC. His first seizure was an afebrile tonic-clonic occurring at the age of 7 years. This subsequently progressed to episodes of burning sensations in his left greater toe followed by tonic-clonic seizures. Within six months he developed four types of seizures: i) Sudden onset, stimulus sensitive rigid feeling of left leg and foot with jerks; at the time of evaluation this had become continuous over many years and resulted in difficulty in walking. ii) Sudden single jerk in left hand (once a day). iii) Onset of dizziness, followed by left facial jerks, then left upper and lower limbs without loss of consciousness (3-4 times per week). iv) Commencing as type two and three but progressing to generalised tonic-clonic convulsions (2-3 times per week).

Clinical Examination: The patient showed continuous jerking of the left leg, particularly involving the toes, associated with hypertonia in the left leg. A left spastic gait was also noted.

Neuroimaging: A standard epilepsy protocol 1.5T MRI was normal. A FDG-PET study showed a marked reduction of uptake over the right hemisphere.

Neurophysiological EMG assessment: The study showed normal upper limb central conduction, and delayed central conduction.

Video scalp Telemetry: The interictal EEG showed continuous theta slowing and frequent epileptiform abnormalities over the right frontotemporal region (Figure 1E). During sleep, intermittent bursts of polyspikes were recorded bilaterally over central and frontocentral regions with a right sided emphasis, associated with muscle artefacts. Multiple episodes of simple partial seizures, characterised by intermittent jerking of the entire left lower extremities were recorded. The jerks were more evident with an external stimulus such as touching the

limb. Video semiology confirmed extra-temporal seizures of right hemispheric onset, with the right peri-rolandic region most likely to be the ictal onset zone.

Intracranial telemetry: Following implantation of intracranial subdural monitoring electrodes over the medial and lateral right frontal lobe (Figure 1 A, B), his EPCs stopped. Several complex partial seizures were recorded showing a regional onset over the posterior and mid aspect of the frontal lobe. Single pulse electrical stimulation (SPES) elicited abnormal delayed responses over the medial and lateral aspects of the frontal lobe, indicating hyperexcitability and potential epileptogenicity of this lobe.¹²

Chronic Cortical Stimulation: Two months after the intracranial telemetry, EPC had re-started and two implantable neurostimulation leads (Medtronic 3986A Resume TL) were inserted under the dura over the mid posterior aspect of the right frontal lobe (Figure 1 C, D) (Figure 2 C,D) and connected to a neurostimulator (Medtronic ActivaPC) implanted at the chest. Intraoperative electrocorticography recordings identified epileptiform discharges over the implanted area. During a telemetry period of 4-days with continuous cortical stimulation at 450 microseconds pulse duration, frequency of 60 Hz, and intensity of 3 mA, the EPC was resolved and no clinical seizures were seen. Stimulation was not perceived by the patient.

Follow up: The patient was seen every month after implantation. From the first month, he reported a reduction (>90%) in the frequency of self-limited seizures, and periods of 30 days without seizures which he had never had before since the beginning of the epilepsy. His gait was markedly improved and he was able to walk without assistance. After 6 months, a change in DBS frequency from 60 Hz to 130 Hz was associated with larger periods without seizures. After 9 months, EPC re-started when a 20% reduction in stimulation intensity was tried with the aim of saving battery power. EPC resolved when the previous stimulation intensity was resumed. A one-day video EEG performed at 12-month follow up showed no subclinical or clinical seizures and the interictal record appeared much improved compared to previous scalp telemetries (Figure 1F), with a significant reduction (>90%) in the incidence of interictal discharges. Sixteen months after implantation the batteries depleted and the EPC restarted.

Four months after replacement with rechargeable batteries (Medtronic ActivaRC) the EPC resolved and the self –limited seizures were reduced by >90%.

Case 2

Clinical History: A 20 year-old left handed male who developed cyanosis following vacuum assisted delivery. Development was normal until 10 months of age when he suffered multiple seizures, up to 40-50 per day, in the form of right facial twitching, right eye blinks; right upper and lower limb sudden flexion followed by rhythmic jerks of the right arm. The seizures have remained unchanged since childhood onset. At one year he developed post-ictal Todd's paresis which persisted for 4 months and gradually improved over many years. Vagus nerve stimulation was attempted with 50% reduction in seizure frequency.

Clinical Examination: Clinical examination revealed EPC on the right upper and lower limb, subtle right hemiparesis with clumsiness of the right hand, otherwise normal tone and cortical sensation.

Neuroimaging: MRI showed focal volume loss across the left central sulcus region associated with white matter signal change, consistent with previous ischaemia.

Scalp Video Telemetry: Interictal EEG during telemetry revealed frequent epileptiform abnormalities over the left anterior temporal region (Figure 2E) with bursts of generalised polyspikes during sleep. Simple partial seizures were associated with rhythmic sharp waves (1Hz) over the midline and left centro-parietal region consistent with his MRI findings.

Intracranial Telemetry and acute cortical stimulation: A 64-contact mat, four 8-contact subdural strips and three depth electrodes were placed over the left frontal and parietal lobes (Figure 2 A, B). Almost continuous interictal discharges and frequent seizures with regional onset were seen over the posterior lateral aspect of the left frontal lobe, Single pulse electrical stimulation and functional mapping with electrical stimulation confirmed that the seizure onset was located in the hand and wrist area. High frequency stimulation was then tried during 4 days (130Hz, pulse width 50 microseconds and up to 2mA). Periods of continuous stimulation of 8-15 hours

were compared with similar time periods with the stimulation off. The cortical stimulation periods showed an approximately 50% reduction of seizure frequency and inter-ictal discharges. As the significant reduction in seizure and interictal activity suggested efficacy of this approach, chronic cortical stimulation was offered.

Chronic Cortical Stimulation: Two implantable neurostimulation leads (Medtronic 3986A Resume TL) were inserted under the dura over the posterior aspect of the left lateral frontal cortex (Figure 2 C,D) and connected to a neurostimulator (Medtronic ActivaPC) implanted at the chest. Intraoperative electrocorticography recordings identified epileptiform discharges over the implanted area. After implantation, a telemetry period of 5 days was used to identify the best cortical stimulation parameters. The stimulation parameters that appeared to be more effective were: 450 microseconds pulse duration, frequency of 130 Hz, and intensity of 3 mA. Using these parameters, the EPC was resolved with a significant reduction (>90%) in the severity and number of the myoclonic jerks. Right arm function was significantly improved, and the patient was able to carry out fine movements previously unseen for years such as drawing and writing. The stimulation was not perceived by the patient.

Follow up: EPC resolved immediately after the onset of stimulation (Figure 2F) and the patient was seen every month after implantation. After one month, the patient reported a >90% improvement in the frequency of self-limited seizures. When the stimulator battery depleted at 10 months, EPC restarted and the patient had several episodes of status epilepticus with motor seizures followed by tonic clonic seizures. After replacement of the cortical stimulation battery, EPC resolved and the self-limited seizures were reduced by more than 90%. This effect has been sustained at 22 month follow- up.

Discussion

The two patients included in this study had EPC arising from the primary motor eloquent cortex of the left leg or of the right hand. At present, no other patient has been treated with chronic

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2
3 cortical stimulation for this condition at our centre. One patient temporarily improved after the
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5 implantation of the intracranial electrodes for the localisation of seizure onset, and the other
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7 one during an initial short trial of continuous stimulation. After implantation of a chronic
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9 stimulator, the EPC resolved for follow-up periods of 9 and 16 months in both patients. When
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11 the DBS batteries ran out of power or when stimulation intensity was reduced by more than
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13 20%, EPC re-started in both cases. After changing batteries or increasing stimulation intensity,
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15 EPC resolved (follow up of 22 months) without side effects. No morbidity was related to the
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17 investigation or implantation phases. Our experience echoes that of previous reports with a
18
19 total of five patients of whom four went on to have successful implantation.^{8,9,10}

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21 The mechanisms of action of cortical stimulation in patients with epilepsy remain unknown. It
22
23 has been suggested that cortical stimulation provokes a reversible functional lesion, inhibiting
24
25 the triggering and/or propagation of epileptic activity from the area of stimulation.¹³ Indeed,
26
27 cortical stimulation with single pulses can provoke long periods of suppression in cellular
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29 firing,¹⁴ suggesting that repetitive stimulation at the correct frequency may be able to suppress
30
31 cortical activity. Furthermore, when cortical stimulation was reduced or stopped there was a
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33 period of several hours/days without EPC in both our patients. This may imply that cortical
34
35 stimulation induces brain neuromodulation, modifying cortical excitability in addition to the
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37 suppressing effect of stimulation for seizure generation. Indeed, recent advances in chronic
38
39 continuous recordings have allowed the development of **closed loop** methods, where
40
41 stimulation starts after an impending seizure is detected.^{15,16,17} Once stimulation achieves
42
43 control of EPC, **closed loop** systems will spare battery power and unnecessary brain stimulation
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45 during the delay period before EPC re-starts.

46 47 Conclusion

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49 We report two cases of medically refractory epilepsy partialis continua responsive to
50
51 implantation of cortical stimulators. No adverse effects were noted and beneficial effects were
52
53 sustained at 22 months follow-up. These findings open up avenues for the treatment of this
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55 difficult and debilitating condition.
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Disclosure

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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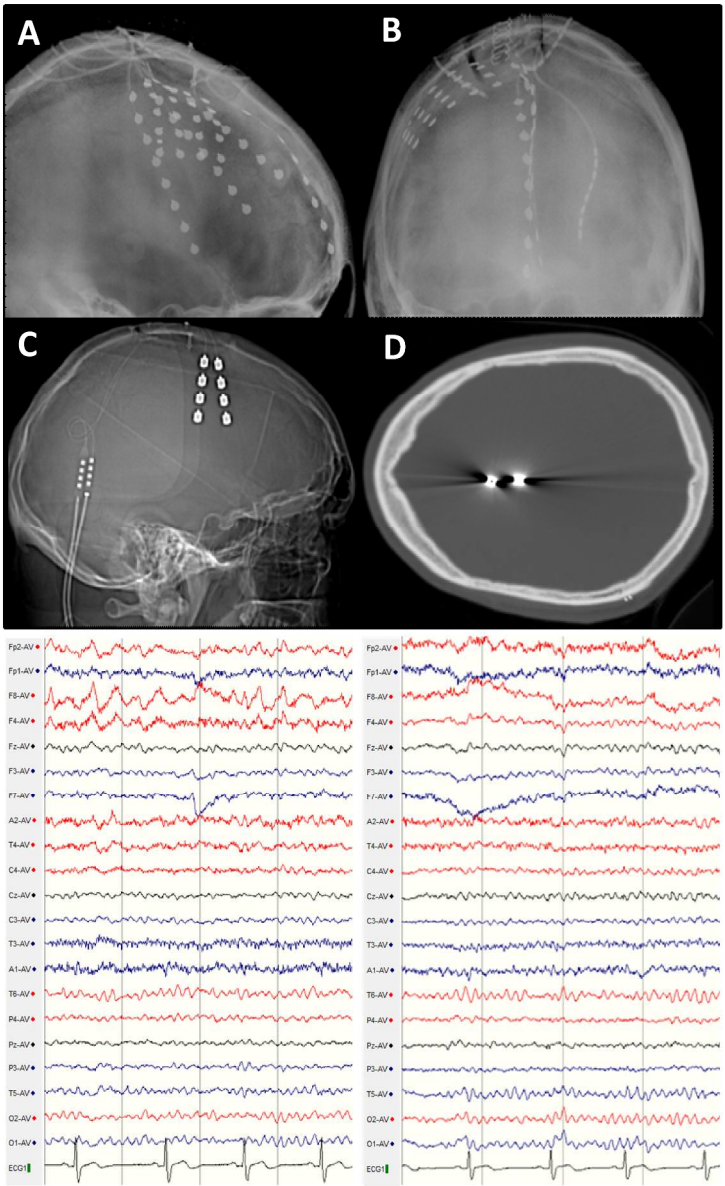
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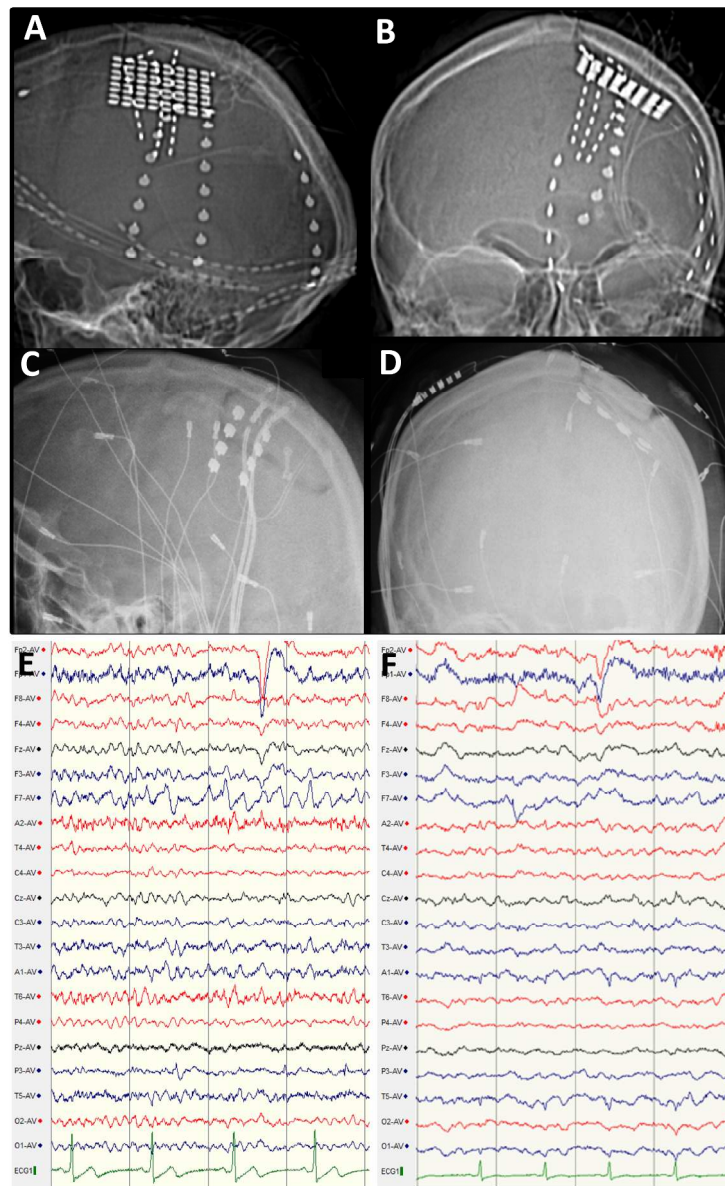
Figure 1: Subdural electrode positions in patient 1. A) Lateral and B) anterior-posterior X-ray images showing intracranial subdural monitoring electrodes over the medial and lateral right frontal lobe. C) lateral X-ray and D) CT showing two subdural electrodes permanently implanted for cortical stimulation over the mid posterior aspect of the right frontal lobe. E) Pre-implantation awake scalp EEG recording. Note the incidence of continuous epileptiform discharges at contact F8. F) Post-implantation awake scalp EEG recording.

Figure 2: Subdural and depth electrode positions in patient 2. A) Lateral and B) anterior-posterior X-ray images showing intracranial subdural mat, strip and depth electrodes over the medial and lateral left fronto-parieto-occipital lobes. C) lateral and D) anterior-posterior X-ray images showing two subdural electrodes permanently implanted for cortical stimulation over the posterior aspect of the left frontal lobe. E) Pre-implantation awake scalp EEG recording. Note the incidence continuous epileptiform discharges at contact F7. F) Post-implantation awake scalp EEG recording.



Subdural electrode positions in patient 1. A) Lateral and B) anterior-posterior X-ray images showing intracranial subdural monitoring electrodes over the medial and lateral right frontal lobe. C) lateral X-ray and D) CT showing two subdural electrodes permanently implanted for cortical stimulation over the mid posterior aspect of the right frontal lobe. E) Pre-implantation awake scalp EEG recording. Note the incidence of continuous epileptiform discharges at contact F8. F) Post-implantation awake scalp EEG recording.

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Subdural and depth electrode positions in patient 2. A) Lateral and B) anterior-posterior X-ray images showing intracranial subdural mat, strip and depth electrodes over the medial and lateral left fronto-parieto-occipital lobes. C) lateral and D) anterior-posterior X-ray images showing two subdural electrodes permanently implanted for cortical stimulation over the posterior aspect of the left frontal lobe. E) Pre-implantation awake scalp EEG recording. Note the incidence continuous epileptiform discharges at contact F7. F) Post-implantation awake scalp EEG recording.

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